be caused by extensive inflammation that results in energy being diverted from anabolic pathways to inflammatory cells. Interestingly, upregulation of NF-κB signaling does not result in hypoglycemia but in the opposite, that is, insulin resistance leading to increases in blood glucose and insulin (Hotamisligil, 2006). This is consistent with the inability of *RelA* haploinsufficiency to rescue the hypoglycemic phenotype of *Sirt6*$^{-/-}$ mice during the first few weeks after birth. The precise biological role of SIRT6 in the regulation of NF-κB thus remains unclear. Although SIRT6 dampens NF-κB-dependent gene expression, it may not be a specific inhibitor of the NF-κB pathway. The initial trigger resulting in the phenotype of *Sirt6*$^{-/-}$ mice is unlikely to be the direct result of disrupting negative control of the NF-κB system. These considerations suggest an alternative explanation of the data, namely that loss of SIRT6 could result in NF-κB-independent nonlethal abnormalities that are then greatly exacerbated by the upregulation of NF-κB target genes, resulting in multiorgan failure and death. What might these abnormalities be? The uniform kinetics of multiorgan deterioration and death in *Sirt6*$^{-/-}$ mice (which die 20–28 days after birth) suggest that *Sirt6* deletion disrupts a crucial transition at a precise stage of postnatal development. In this light, it is worth noting that *Sirt6*$^{-/-}$ mice show an erosive colitis resulting in death around the time of weaning, when the gut microbiota undergoes major changes. Thus, one interesting possibility is that the erosive colitis found in *Sirt6*$^{-/-}$ mice predisposes them to intestinal infections at a time when the immune-protective role of maternal milk has ceased and new microbes are introduced into the gut with food. Under these conditions of infection at an extensively eroded mucosa, deregulation of NF-κB target gene expression (which results in excessive inflammation) may lead to a lethal outcome. Consistent with this notion, the phenotypic rescue due to *RelA* haploinsufficiency is also observed at this stage of mouse postnatal development and not in the first 3 weeks after birth.

Microbe-triggered inflammatory responses evolved in multicellular organisms and are essential for survival. Successful antimicrobial responses require that energy sources be redirected from other biological processes (such as anabolic pathways) to support the activities of inflammatory cells; NF-κB and SIRT6 are two essential components of this interface between metabolism and inflammation. The Kawahara et al. study now suggests that these two proteins connect inflammation and metabolism to aging-associated gene expression programs, thus providing a busy crossroads for several key pathways.

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Are GTGs ABA's Biggest Fans?

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The search for receptors for abscisic acid (ABA), a phytohormone central to the response of plants to biotic and abiotic stress, has been controversial. In this issue, Pandey et al. (2009) report the identification of two membrane proteins from *Arabidopsis*, GTG1 and GTG2, that bind ABA in vitro and mediate ABA responses in vivo.

Abscisic acid (ABA) is a phytohormone that serves as the prime signal in the responses of plants to environmental stress imposed by cold, drought, or high levels of salts (Christmann et al., 2006). Given its importance for plant physiology, identifying the hormone's receptors has been a long-standing objective. Although a number of different proteins have been suggested to act as ABA receptors, the findings have been contested and in one case recently retracted (Razem et al., 2008). In this issue, Pandey et al. (2009) link two membrane proteins with homology to G protein-coupled receptors (GPCRs),

GTG1 (GPCR-type G protein 1) and GTG2, to specific effects of ABA exposure including stomatal closure and inhibition of germination and root growth. Even more tantalizing, they also provide evidence that GTG1 and GTG2 directly bind ABA in vitro, thereby proposing that the two proteins are ABA receptors.

Prior work had already established links between G proteins and ABA signaling, with defects in subunits of heterotrimeric G proteins altering ABA responses. *Arabidopsis* has only one canonical Gα subunit (GPA1), and loss of GPA1 causes ABA-hypersensitive inhibition of growth and germination (Pandey et al., 2006). The connection between G protein signaling and ABA responses is strengthened by the authors' current work. GTG1 and GTG2 have predicted homology to rhodopsin-like GPCRs (Bhasin and Raghava, 2005) and are unique among eukaryotic GPCRs in that they have an inherent GTPase activity resulting from a functional fusion of a predicted GPCR and a G protein. Moreover, they show that both GTG1 and GTG2 physically interact with GPA1.

Pandey et al. use genetics to establish a role for GTG1 and GTG2 in ABA signaling. Although loss of either GTG1 or GTG2 function did not have phenotypic consequences (which suggests they might be functionally redundant), the loss of both proteins resulted in hyposensitivity to ABA. This included impairment of ABA's effects on stomata, germination, and growth inhibition. The authors then provide evidence that GTG1 and GTG2 bind to ABA and thereby might be ABA receptors. ABA exists as two enantiomeres, S-ABA (Figure 1A) and R-ABA. Although ABA biosynthesis generates only the physiologically active S-ABA form, R-ABA has proven to be active in several ABA responses as well. The binding of GTG1 and GTG2 to ABA is shown to be stereoselective, that is, the two proteins only bind S-ABA. This stereoselectivity is consistent with the claim that the proteins are ABA receptors. Moreover, the dissociation constant of approximately 40 nM observed in their in vitro binding assays falls in the range of resting ABA levels.

Although the ABA responses of plants lacking both GTG1 and GTG2 were impaired, they were not abolished. This suggests the existence of an alternative ABA signaling pathway independent of GTG1 and GTG2 receptor function. An alternative possibility is that GTG1 and GTG2 may not act as receptors but rather as modulators of ABA responses. Other evidence points to the existence of ABA signaling pathways that do not involve GTG1 and GTG2, in particular as it relates to guard cells, which control the opening and closing of stomata to regulate gas exchange. To execute ABA-triggered stomatal closure, an efflux of anions is required for the depolarization of guard cells, allowing for the activation of a cation efflux. Electrophysiological analyses of guard cells support the existence of both a plasmalemma-localized site of ABA perception (Hamilton et al., 2000) and intracellular ABA receptor(s) (Levchenko et al., 2005). When ABA is administered externally to guard cells, the activation of anion channels is delayed compared to intracellular administration. This finding favors a model whereby ABA in guard cells is perceived intracellularly, whereas GTG1 and GTG2 are shown by Pandey et al. to reside on the plasma membrane.

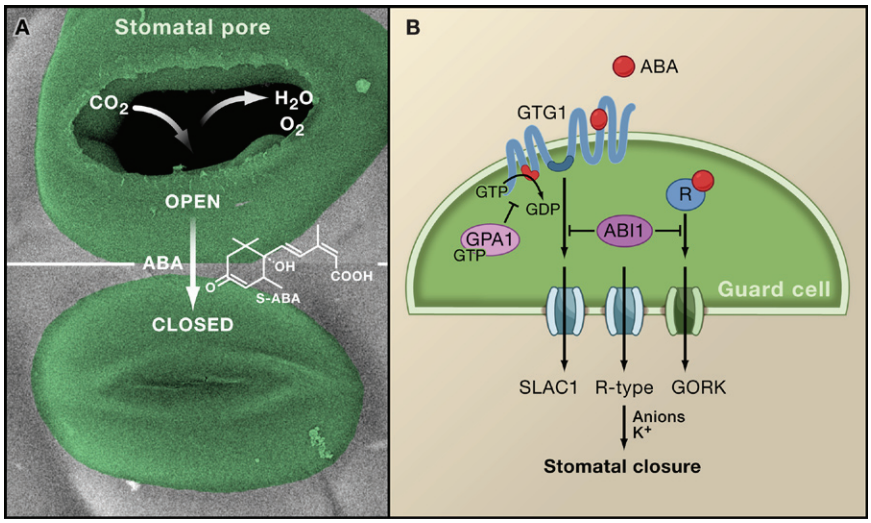

Figure 1. GTG1 and GTG2 in Abscisic Acid Signaling

(A) A pair of guard cells from a leaf stomatal pore. Osmoregulated swelling and shrinking of guard cells control stomatal aperture and gas exchange. The phytohormone abscisic acid (ABA) induces stomatal closure by mediating solute loss from guard cells. Photograph kindly provided by Dr. P. Walther.

(B) Model of GTG action in the ABA-induced stomatal closure. Upon ABA binding, GTG1 and GTG2 activate anion efflux from guard cells via the slow-type anion channel SLAC1 and the rapid-type channel (R-type), which has not yet been molecularly identified. Depolarization of guard cells allows activation of a cation efflux via the guard cell outward-rectifying potassium channel (GORK), resulting in water loss, to induce stomatal closure. The ABA response is negatively regulated by the protein phosphatase ABI1, a key regulator of early steps in the ABA signal transduction. ABI1 also counteracts signaling by an unknown cytoplasmic ABA receptor R. The GTPase activity of GTGs is inhibited by the GTP-bound Gα subunit GPA1. The ATP-/GTP-binding region of GTG1 is in the proximity of the carboxy-terminal end and is marked in red, while the region with similarity to Ras GTPase-activating protein domain is highlighted in blue.

Interestingly, a structural human homolog of GTG1 and GTG2, GPHR (Golgi pH regulator), has recently been shown to be an anion channel involved in ion homeostasis of the Golgi (Maeda et al., 2008). It is therefore tempting to speculate that GTG1 and GTG2 might be ABA-regulated anion channels. There are two types of anion channels activated by ABA, a slow type and a rapid type (Figure 1B). The identity of the slow anion channel is known and has an unexpected similarity to organic acid transporters (Vahisalu et al., 2008). In contrast, the identity of the rapid anion channel involved in ABA-induced stomatal closure is still unknown. Electrophysiological analyses of guard cells deficient in GTG1 and GTG2 could address whether or not these are the elusive rapid-type ABA-regulated anion channels.

In having both GDP- and GTP-binding capacity and several membrane-spanning domains (8–10 predicted, more than the 7 of prototypical GPCRs), GTG1 and GTG2 are reminiscent of the bacterial iron uptake system involving FeoB. Like GTG1 and GTG2, FeoB has a preference for GDP binding over GTP (Eng et al., 2008),

although the regulatory role of GDP versus GTP binding is unknown. Using a constitutively active form of GPA1 (which does not require GTP for activation), Pandey et al. have elegantly shown that the interaction of the GTG proteins with GTP-GPA1 inhibits their GTPase activity. The regulation of a GPCR-type protein by GTP-GPA1 is unprecedented. If GTG1 and GTG2 act like regular GPCRs, one would expect that ABA perception leads to GTP-GPA1 formation, which subsequently inhibits GTG1 and GTG2 GTPase activity. This finding is, however, difficult to reconcile with the *gpa1* and *gtg1 gtg2* single or double mutant phenotypes. Indeed, GPA1 and GTGs play different roles in stomatal regulation. GPA1 is required for inhibition of stomatal reopening by ABA, whereas GTG1 and GTG2 are required for ABA to induce stomatal closure. The occurrence of epistatic interactions in a *gpa1 gtg1 gtg2* triple mutant would provide evidence that GPA1 and the GTGs indeed act in the same signaling pathway, as implied by the biochemical analyses. In the current study, GTP-GPA1 is proposed to function as a rheostat downregulating ABA binding to GTGs. Binding of ABA to GTG1 and GTG2 did not affect their GTPase activity; however, the analyses were performed with purified proteins and only approximately 1% of GTG1 and GTG2 were functional in binding the phytohormone. Expression and functional analysis of GTG1 and GTG2 in a more physiological environment, such as membranes of an organism or cells devoid of an ABA signal pathway, could uncover their mode of regulation.

The identification of GTG1 and GTG2 reveals fascinating insights into a new class of integral membrane-localized G proteins of eukaryotes. The prediction that they represent ABA receptors will undoubtedly motivate further study. Future work establishing a robust link to central components of the ABA signaling pathway could bolster the claim that GTGs are ABA receptors. Such components would, for example, include the homologous protein phosphatases ABI1 and ABI2, which are key regulators of early steps in the ABA signal transduction cascade.

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A New Family of Odorant Receptors in *Drosophila*

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In the fruit fly *Drosophila*, not all olfactory sensory neurons express a seven transmembrane odorant receptor, suggesting that other types of odorant receptors might exist. Benton et al. (2009) now present evidence that a family of proteins related to ionotropic glutamate receptors is a previously unrecognized class of odorant receptors.

Odor detection is accomplished by odorant receptors, originally identified in rodents as a large family of seven transmembrane G protein-coupled receptors (GPCRs). Odorant receptors have subsequently been found in fish and nematodes, and eventually in the fruit fly *Drosophila* (Bargmann, 2006). Surprisingly, *Drosophila* seven transmembrane odorant receptors (ORs) were recently found to have inverted membrane topology compared to typical GPCRs, with their N terminus facing the cytoplasm rather than the extracellular space (Benton et al., 2006). Additionally, *Drosophila* ORs require Or83b, another seven transmembrane protein highly conserved in insects, as an obligate coreceptor (Lars-